Azzato EM, Chen RA, Wacholder S, Chanock SJ, Klebanoff MA, Caporaso NE. Maternal EPHX1 polymorphisms and risk of phenytoin-induced congenital malformations. *Pharmacogenet Genomics*. 2010;20(1):58-63.

Abstract: ***Objectives:*** The teratogenic effects of the anti-epileptic drug phenytoin have been linked to genetic differences in phenytoin disposition. The goal of this study was to assess the effect of maternal genotype of functional polymorphisms in two genes involved in phenytoin metabolism, CYP2C9 (R144C, I395L) and EPHX1 (Y113H, H139R), on the presence of major craniofacial abnormalities (CFAs) in the child. ***Methods:*** We used data from the Collaborative Perinatal Project (1959-1974), a study involving 42 000 mothers and 55 000 children to assess the effect of maternal genotype. We studied 174 pregnancies in 155 women who used phenytoin throughout their pregnancy, gave birth to a live child and had available stored blood specimens suitable for DNA extraction. ***Results:*** Nineteen children had CFA. In a logistic regression model adjusted for history of phenytoin use during the first trimester and maternal epilepsy (N=157 pregnancies), the maternal EPHX1 113 H [per rare allele odds ratio (OR): 2.43, 95% confidence interval (CI): 1.16-5.10, P=0.02] and 139 R (per rare allele OR: 2.33, 95% CI: 1.09-5.00, P=0.03) alleles were associated with CFAs in the child. The maternal EPHX1 Y113/H139 (common) haplotype showed a significant protective association with CFAs in the child (OR: 0.29, 95% CI: 0.12-0.68, P=0.004), when compared to other haplotypes. CYP2C9 genotype was not related to fetal endpoints. ***Conclusion:*** Maternal EPHX1 genotype may be associated with risk of fetal anomalies among pregnant women taking phenytoin. Future study is required to confirm these results in larger, independent populations.